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A Two-stage Dynamic Model to Enable Updating of Clinical Risk Prediction from Longitudinal Health Record Data: Illustrated with Kidney Function

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Abstract

We demonstrate the use of electronic records and repeated measures of risk factors therein, to enable deeper understanding of the relationship between the full longitudinal trajectory of risk factors and outcomes. To illustrate, dynamic mixed effect modelling is used to summarise the level, trend and monitoring intensity of kidney function. The output from this model then forms covariates for a recurrent event Cox proportional hazards model for predicting adverse events (AE). Using data from Salford, UK, our multivariate model finds that steeper declines in kidney function raise the hazard of AE (HR: 1.13, 95% CI (1.05, 1.22)). There is a non-proportional relationship between the hazard of AE and the monitoring intensity of kidney function. Neither of these variables would be present in a classical risk prediction model.. This work illustrates the potential of using the full longitudinal profile of risk factors, rather than just their level. There is an opportunity for deep statistical learning leading to rich clinical insight using longitudinal signals in electronic data.

Keywords:

Biomarkers; Clinical Prediction; Estimated Glomerular Filtration Rate; Longitudinal Analysis; Model Calibration.

Introduction

Most risk prediction models incorporate only the most recently measured value of a biomarker or risk factor. This is often inadequate as risk may be driven by decline, variability, or other complex aspects of the longitudinal trajectory. Electronic medical records contain rich longitudinal data from which risk factor trajectories can be estimated, and therefore used to enrich prediction models. In this paper we present an example of a two-stage model that first estimates the longitudinal trajectory of a risk factor, then uses predictors derived from this in a risk prediction model.

We illustrate the model using the example risk factor of estimated glomerular filtration rate (eGFR), which is a measure of kidney function. Deteriorating kidney function is an important risk factor for adverse events. Chronic heart failure (CHF) and type 2 diabetes (T2DM) both damage the kidneys. CHF reduces blood flow through the kidneys due to weaker heart pumping; the factors causing it also affect the kidney blood vessels; and some CHF treatments may damage the kidney. T2DM damages the blood vessels and other parts of the kidney directly. So, patients with these conditions require particularly diligent monitoring of their regular laboratory test results.

Kidney disease in patients with T2DM is well documented in the literature. A recent study in the US showed that as many as 43.5% of patients with T2DM have chronic kidney disease (CKD) [1]; CKD is strongly associated with increased mortality and accelerated cardiovascular disease [2]. Patients with T2DM are also more likely to experience acute renal failure than patients without diabetes (adjusted hazard ratio: 2.5, 95% CI 2.2 – 2.7) [3]. Like CKD, acute renal failure is also associated with high mortality rate, around 50% [4].

Data from the EuroHeart Failure survey suggest that patients with T2DM and impaired kidney function have amongst the worst short and long-term outcomes [5]. A recent study [6], showed that the combination of poor heart and kidney function is a particularly strong and discrete risk factor for death. Another study [7] found that T2DM was a statistically significant predictor of all-cause mortality in patients with CHF, but only those who had eGFR between 30 and 90 ml/min*1.73m^2. Heart and kidney dysfunction are closely linked [8] and diabetes worsens the situation, whether measured by hospital admissions or death rates [9].

In addition to slowly progressing disease, the kidneys can suffer acute injury leading to emergency hospitalisation and death, especially among patients with CHF and T2DM. Most reported studies in this area have focused on measuring kidney function at the time of endpoints such as death or admission. This study shifts the focus to the *process* of deteriorating kidney function itself. The aim is to examine in detail the trajectory of eGFR prior to endpoints being observed. In particular we will consider the effects of eGFR level, rate of decline and intensity of monitoring on adverse events such as emergency hospitalisation rates and all-cause mortality in patients with CHF and T2DM.

Methods

The data used in this study were obtained from the Salford Integrated Record (SIR) – a medical data store in Salford, Greater Manchester, UK. The population of Salford is around 234 thousand with 53 general practices and a single hospital. SIR contains linked data from both primary and secondary care for the population that engage with health services.

The cohort was restricted to patients who had both CHF and T2DM. Patients with congenital heart disease and those with cor pulmonale were excluded from the study, as were patients who had renal replacement therapy during the study period, where eGFR has a different interpretation. The study period spanned from January 2008 to August 2012.

The main outcome of interest was adverse events (AE), which comprise emergency hospital admissions and all-cause mortality. The covariates of primary interest were eGFR level, rate of decline and intensity of monitoring. Models were corrected for patient's age at the time of follow-up start, gender, and index of multiple deprivation (IMD) 2010. All covariates related to

eGFR are time dependent and as such require estimation of the longitudinal process for each patient. Therefore we take a two stage modelling approach. In Stage 1, the eGFR process is estimated. Stage 2 then models AEs as a function of the eGFR process.

For Stage 1, a simple approach to estimating the eGFR level at any time, t, is to use either the most recent eGFR value or some summary of a collection of recent eGFR values like the median or the mean. The eGFR decline can be calculated as the difference between the last and the penultimate eGFR values. In both cases, one needs to make several, rather arbitrary, decisions, for example, decide how far apart the two eGFR values should be in the case of calculating the eGFR decline. Also, as eGFR values can be 'noisy', this approach can be affected by variations in eGFR values. In order to smooth the variation in eGFR values and use all of the information about the degradation process of the kidney function in this particular population, we used dynamic mixed effects regression [10-11]. The eGFR level and decline for each patient at any given point in time t, was derived from a mixed effects model fitted to all of the eGFR data prior to t. The generic model was formulated as follows: dependent variable – the logarithm of eGFR, predictors (fixed effects) – age, gender, IMD, time since diagnosis (TSD) and time since study start (TSS), and random effects – variance of random effects on the intercept and coefficient of TSS.

For each patient at each endpoint at time t, eGFR level was measured by the predicted eGFR value at time t and eGFR decline was measured as $(a - b) / (t - t_a)$, where a is the predicted eGFR value at the start of the study, t_a, and b is the predicted eGFR value at time t. Since the kidney function for the cohort considered in this study is in progressive decline, for all $t > t_a$ the eGFR slope is a positive number, where higher values indicate steeper decline.

The eGFR intensity of monitoring was measured as the proximity of the most recent eGFR record: within 180 days, between 180 and 365 days and more than 365 days.

For Stage 2, modelling the risk of AE, we used a repeated measures Cox proportional hazards (CPH) model with gamma shared frailty – i.e. patient level random effects were modelled using a gamma distribution [12]. CPH model is a popular method used to model survival data [13-14]. It is a semi-parametric method with an advantage over parametric methods in that it focuses on hazard ratios only, thus, bypassing the need to specify a parametric distribution for the baseline hazard. This allows direct comparison of the risk between subjects with different characteristics, where a hazard ratio of one indicates that there is no difference in risk; ratios above one indicate higher risk; and below one lower risk.

Results

The process of deriving the cohort is illustrated in Figure 1.

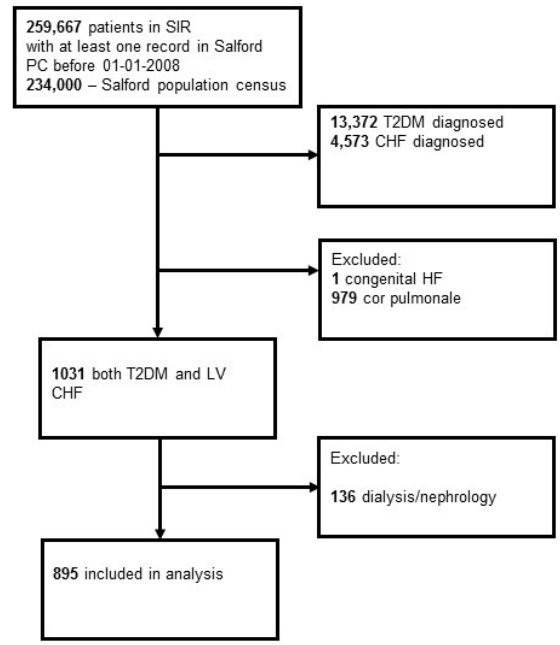

Figure 1 – Exclusion flowchart.

Stage 1

Table 1 shows exponentiated fixed effects of two log eGFR mixed effects models. The first model is the model fitted for the first AE during the study period. It is the model that used the smallest number of eGFR records for estimating the kidney function decline process. For each subsequent event, this model was updated with more data until the last model, which was fitted at the end of the study. Time is measured in years. From Table 1 we can note that older patients tend to have lower eGFR, female patients have lower eGFR than male patients, patients who have had both CHF and T2DM for longer have lower eGFR, and the eGFR is in decline with time.

Figure 2 shows the random effects of each patient on the intercept and the coefficient of the TSS for the last model. For the intercept, patients with negative random effects have lower than average eGFR. For the slope, patients with negative random effects have steeper than average decline in eGFR. We can see from Figure 2 that most of the steeper decline in eGFR is associated with patients with below average eGFR. The predicted eGFR levels and declines where carried forward to Stage 2.

Table 1 – Exponentiated parameter estimates of log eGFR models. Interpretation example: male coefficient is greater than one, meaning male eGFR is predicted to be higher.

	First model	**Last model**
Intercept	139.5 (119.72, 162.56)[a]	146.01 (126.47, 168.56)[a]
Age	0.99 (0.99, 0.99)[a]	0.99 (0.99, 0.99)[a]
Gender:		
Female	1	1
Male	1.07 (1.03, 1.11)[a]	1.05 (1.01, 1.1)[a]
Time since diagnosis	0.98 (0.98, 0.99)[a]	0.98 (0.98, 0.99)[a]
Time since study start	0.96 (0.95, 0.98)[a]	0.97 (0.97, 0.98)[a]

Key: a – statistically significant at 5%

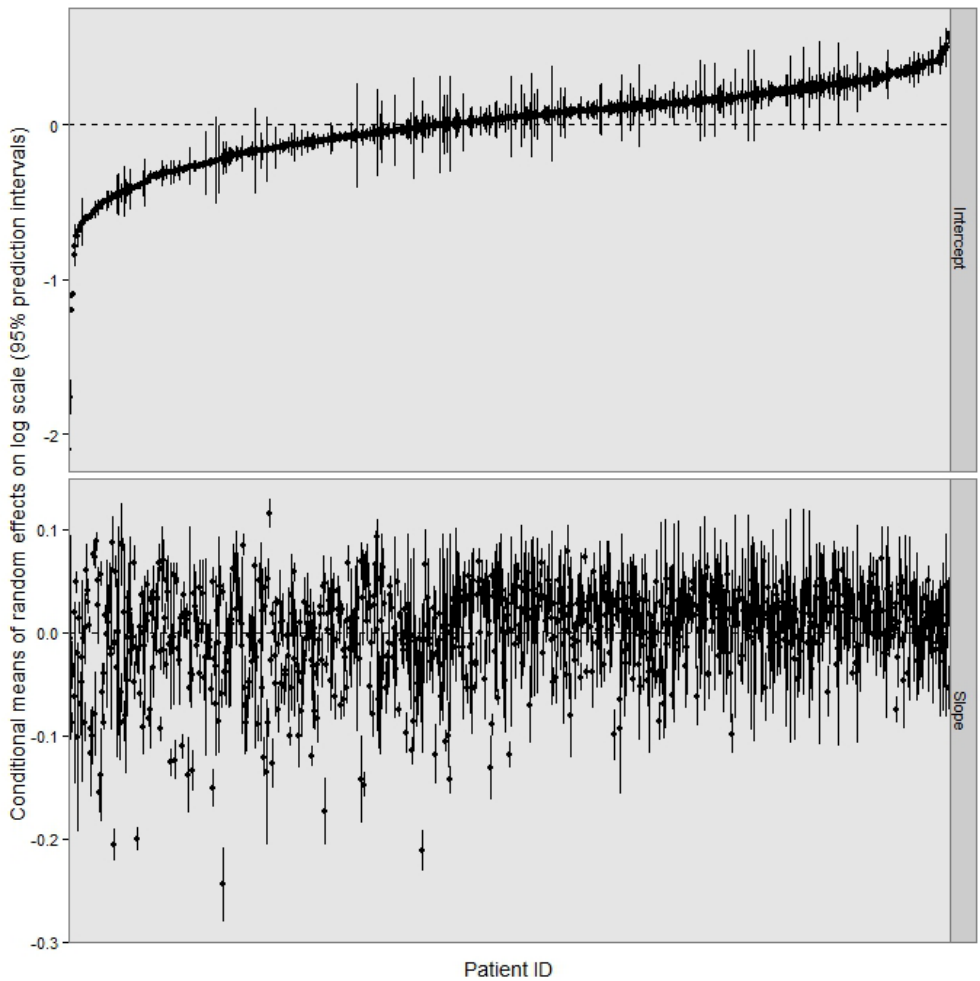

Figure 2 – Patient random effects on the intercept and on the slope of time since study start [15].

Stage 2

Table 2 shows covariate details and hazard ratios for univariate and multivariate models for AE. We can note the following from the table. Older patients are at higher risk of AE. Gender, IMD and eGFR level were not statistically significant, whereas the eGFR decline was. The hazard ratio for the eGFR decline indicates that a one unit decrease in eGFR per year increases the hazard of AE by 10-11%. The hazard ratios for the eGFR monitoring indicate that patients with more recent eGFR records are more likely to have AE. The multivariate model was selected on the basis of significance of the parameter estimates. The eGFR monitoring covariate failed to adhere to the proportional hazards assumption, so the multivariate model is stratified on this. Kaplan-Meier plots of the eGFR monitoring strata are presented in Figure 3.

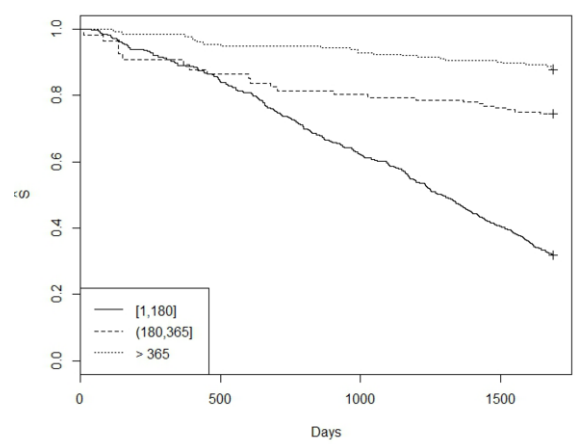

Figure 3 – Kaplan Meier plot of AE-free survival stratified by time since most recent eGFR measurement.

Table 2 – Hazard ratios for emergency hospital admissions models. Hazard ratios greater than one represent higher risk.

Covariates	**Mean (SD), count or proportion**	**Hazard ratio (95% CI)**	
		Univariate	**Multivariate**
Age	73.03 (10.43)	1.02 (1.01, 1.04)[a]	1.03 (1.01, 1.05)[a]
Gender:			
Female	42%	1 (reference)	-
Male	58%	1.2 (0.857, 1.68)	-
IMD 2010	37.16 (18.20)	1 (0.993, 1.01)	-
eGFR level	59.03 (18.18)	0.996 (0.988, 1)	-
eGFR decline	2.27 (2.05)	1.11 (1.03, 1.19)[a]	1.13 (1.05, 1.22)[a]
Last eGFR	58.58 (21.37)	0.993 (0.986, 1)[a]	-
eGFR monitoring:			
[*1, 180*]	730	1	-
(*180, 365*]	149	0.21 (0.12, 0.35)[a]	-
> 365	190	0.13 (0.08, 0.20)[a]	-

Key: a – statistically significant at 5%

Discussion

We have presented a proof-of-concept study of a two-stage framework for modelling the full longitudinal profile of a risk factor and its impact on risk, using the example of eGFR decline in T2DM and CHF patients. We found that eGFR decline, modelled as patient-specific slope from a mixed effects model, was a strong predictor for adverse events (AE), and eGFR level was not a significant predictor either in a univariate or multivariate model. In a standard predictive modelling framework, only the most recent eGFR measurement would have been taken, so eGFR decline would not have been captured. We additionally considered the intensity of eGFR measurement as a predictor, and found a complex relationship between this and AE.

The main strength of this study is the incorporation of longitudinal information from routine care-records into risk prediction, a feature absent from standard models. We considered one risk factor but the method is easily extended to multiple risk factors. The main weakness is that uncertainty in eGFR predictions is not propagated to the estimates of the hazard ratios across the two stages of the method. Future work will investigate joint modelling approaches to overcome this.

We considered only mixed effects regression to model the trajectory of eGFR. Other methods such as random forests, neural networks and support vector regression could be used for this purpose. These machine-learning techniques might better cope with additional covariates, particularly treatments for T2DM and CHF that could influence kidney function. In our data, there were over a thousand different medications prescribed among our patient cohort in the month preceding the first eGFR measurement. Future work will compare alternative dynamic modelling strategies capable of incorporating complex covariate structures.

The ability to monitor and predict longitudinal processes using dynamic models, integrated with medical records, provides an opportunity to develop optimal monitoring polices for these risk factors. Linking the predictions of the kidney function decline to the effectiveness of its monitoring, aimed at averting adverse events, is a hard problem and the subject of ongoing research. This requires investigating the mechanism behind how the decline in eGFR leads to adverse events. For example, it may be that the decline in eGFR first leads to changes in treatment that in turn precipitate adverse events.

As with most routine care-records, the data in our study had limitations. In particular, the linkage of emergency hospital admissions to the SIR database required general practitioners to enter or accept data on admission episodes. In addition, we did not have data on the duration of hospital admissions, which could have been used to refine our endpoint definitions.

Despite limitations in the data and methodology this study has clearly demonstrated that clinical predictive models can improve their predictive abilities by taking account of the longitudinal information in electronic health records.

Consider EU Directive 2007/47 that considers algorithms used for prognostic purposes to be “medical devices.” The usual validation methods for such algorithms certify the encoding into software of models, but rarely question the fact that published model parameters will drift in calibration as risk-factor environments change. In addition, the structure of models may need reconsidering as populations, contexts of healthcare/observation and data-quality evolve.

Conclusion

Sophisticated statistical modelling with electronic health records allows for complex relationships between risk factor trajectories and outcomes to be captured, thereby improving predictions. Most current predictive models do not exploit longitudinal health record information in this way – neither is the regulatory framework for clinical algorithms set up to cope with this dynamic modelling approach. Research is urgently needed into statistical methods and computational frameworks for optimising clinical prediction from the continuously evolving risk information across heterogeneous populations, healthcare environments and information systems.

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